CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER	74912
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ADMINISTRATIVE DOCUMENTS

DIVISION REVIEW SUMMARY

ANDA: 74-912

DRUG PRODUCT: Selegiline Hydrochloride

FIRM: Stason Industrial Corp.

DOSAGE FORM: Tablets

STRENGTH: 5 mg

CONTAINERS: 60 cc/60's & 225 cc/1,000's

CGMP STATEMENT/EIR UPDATE STATUS:

Acceptable, dated 12/6/96 and 3/6/98

BIO INFORMATION:

Acceptable, dated 1/26/98.

VALIDATION

N/A

STABILITY

Lot no. PK5001
-was placed in accelerated and room temperature stability studies (40°C/75% RH) in the proposed marketing container configurations. The stability data submitted are found to conform to the proposed stability specifications. Based upon the stability data submitted the proposed 24 months expiration period is granted.

The container/closure systems are described in the container section of the application (for the 60's and 1,000's).

LABELING

Acceptable, dated 3/23/98.

STERILIZATION VALIDATION

N/A

SIZE OF BIO/STABILITY BATCHES

Selegiline Hydrochloride is manufactured by

The subject DMF was found to be acceptable dated 5/17/97.

A _ lot was manufactured and a total of _ units were The subject lot was completely packaged.

PROPOSED PRODUCTION BATCH

Blank batch records for the maximum intended production batch size of units is appended.

RECOMMENDATION:

Recommend approval of generic drug product Selegiline Hydrochloride Tablets, 5 mg.

SIGNATURE:

<u>DATE:</u> April 8, 1998

REVIEW OF PROFESSIONAL LABELING DIVISION OF LABELING AND PROGRAM SUPPORT LABELING REVIEW BRANCH

ANDA Number: 74-912

Date of Submission: March 10, 1997

Applicant's Name: Stason Industrial Corporation

Established Name: Selegiline Hydrochloride Tablets USP, 5 mg

Labeling Deficiencies:

1. CONTAINER - 60s and 1000s

Satisfactory in draft.

2. INSERT

a. DESCRIPTION

Relocate the chemical formula to either somewhere below, or to the side of, the structural formula.

b. CLINICAL PHARMACOLOGY

Pharmacokinetic Information (Absorption, Distribution, Metabolism and Elimination - ADME), Paragraph five - ...activity as a function...

[Note: "as" rather than "is".]

C. CONTRAINDICATIONS

... (See PRECAUTIONS...

[Note: Precautions Plural.]

d. WARNINGS

Paragraph three - Revise the first sentence to read:

...MAOIs (phenelzine, tranycypromine). A similar...

e. PRECAUTIONS

 Carcinogenesis, Mutagenesis, Impairment of Fertility - Italicize "Salmonella typhimurium".

NO.172

Pregnancy: Teratogenic Effects - Pregnancy Category C.

Please revise your insert labeling, as instructed above, and submit final printed container labels and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Jepry Phillips

Director

Division of Labeling and Program Support

Office of Generic Drugs

Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74912

CORRESPONDENCE

4/22/98 74-912 method (STM.0491) For stability analysis - what is the specified? (Or world you point me to the method description STM.049?) Kethamplelasnine 4/22/98 Called Firm (Monica) + requested that they isperify the assay analysis At was agreed. Fax with info will tollow a 4/23/78.



STASON PHARMACEUTICALS, INC.

11 MORGAN, IRVINE, CA 92718-2005, U.S.A. TEL: (714)380-4327 FAX: (714)380-4345

April 22, 1998

Mr. Edwin Ramos
Chemistry Reviewer
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

vìa facsimile (301) 443-3839

NEW COPRESP

NC

RE: Selegiline Hydrochloride Tablets, USP 5mg ANDA 74-912

TELEPHONE AMENDMENT

Dear Mr. Ramos:

Reference is made to the telephone conversation on April 22, 1998 regarding ANDA 74-912 for Selegiline Hydrochloride Tablets, USP 5 mg.

The requested information is as follows:

An updated copy of the Standard Testing Method will be included in the annual report. If you require additional information, please call me at (714) 380-4327 ext. 235 or fax me at (714) 380-4345.

Sincerely,

Monica Tinio

Manager, Regulatory Affairs Stason Pharmaceuticale, Inc.

\$1:ANDA:Sel:Edwin



STASON PHARMACEUTICALS, INC.

11 MORGAN, IRVINE, CA 92718-2005, U.S.A. TEL: (714)380-4327 FAX: (714)380-4345

February 25, 1998

Ms. Kassandra Sherrod Project Manager Office of Generic Drugs, CDER, FDA Document Control Room, Metro Park North II 7500 Standish Place, Room 150 Rockville, MD 20855-2773 ARCHIVAL COPY

ORIG AMENDMENT

NAF

RE: Selegiline Hydrochloride Tablets, USP 5 mg ANDA 74-912

FINAL PRINTED LABELING

Dear Ms. Sherrod:

Pursuant to 21 CFR 314.60, we submit herein changes to our package insert due to recent and significant changes in the insert labeling of the listed drug Eldepryl® Tablets (Somerset Pharmaceuticals, Inc.; revised February 1997 and approved August 6, 1997).

We have included twelve (12) final printed package inserts and container labels for your review; eleven (11) copies are in the archival copy and one (1) copy is in the review copy of this application.

Pursuant to the Final Rule published in the Federal Register dated September 8, 1993 and 21 CFR 314.94, Stason Pharmaceuticals, Inc. certifies that a true copy of this submission has been provided to the FDA Los Angeles District Office on the same date of this application to the Office of Generic Drugs.

If you need my assistance in the review of this submission, please call me at (714) 380-4327 ext 235 or fax me at (714) 380-4345.

Sincerely,

Monica Tinio

Manager, Regulatory Affairs

Stason Pharmaceuticals, Inc.

RECEIVED

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GENERIC DRUGS



STASON INDUSTRIAL CORPORATION

11 MORGAN, IRVINE, CA 92718-2005, U.S.A. TEL: (714)380-4327 FAX: (714)380-4345

AMENDMENT

July 31, 1997

Attention: Edwin Ramos
Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

MFA

via facsimile (301)443-3839

Re:

ANDA 74-912, Selegiline Hydrochloride 5 mg Tablets

Reference is made to the telephone conversation on July 31, 1997 regarding ANDA 74-912, Selegiline Hydrochloride 5 mg Tablets.

Enclosed, we have submitted a "TELECOM" AMENDMENT to resolve the issues in the application as set forth in the telephone conversation.

Sincerely yours,

Harry T. Pan

Chief Operating Officer

RECEIVED AUG 0 5 1997 GENERIC DRUGS



STASON INDUSTRIAL CORPORATION

ruted mg

11 MORGAN, IRVINE, CA 92718-2005, U.S.A. TEL: (714)380-4327 FAX: (714)380-4345

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AMENDMENT

11/-12

July 22, 1997

Office of Generic Drugs, CDER Food and Drug Administration Metro Park North II 7500 Standish Place Rockville, MD 20855-2773

Re: ANDA 74-912, Selegiline Hydrochloride 5 mg Tablets

Reference is made to the chemistry and labeling deficiency letter dated July 7, 1997 for ANDA 74-912, Selegiline Hydrochloride 5 mg Tablets.

Enclosed, we have submitted a **MINOR** amendment (Amendment #003) to resolve the deficiencies in the application as set forth in the deficiency letter.

Sincerely yours,

Harry T. Fan

Chief Operating Officer

Alled Firm on 7/30/97 +

Mr. Fan was not available a haft
message For him to return my soll
so we can discuss minor industria
or we can discuss minor industria

714-380-4327 Ext: 222

7/30/97

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material complete is to a few and a second

decision 1/3

~ Vande

THIRD COPY CERTIFICATION

July 22, 1997

Stason Industrial Corporation has provided a field copy of the amendment #003 to the appropriate district office. Stason Industrial Corporation hereby certifies that this copy is a "true" copy of the amendment to the application.

Harry T.*Œ*an

Chief Operating Officer

FACSIMILE AMENDMENT

JUL 7 1991

ANDNAMDA: 74-912

OFFICE OF GENERIC DRUGS, CDER, FDA Document Control Room, Metro Park North II 7500 Standish Place, Room 150 Rockville, MD 20855-2773



TO: APPLICANT Stas on Industrial Corporal PHONE (714) 350-4327
ATTN: Harry T. For FAX (714) 380-4345

FROM: Kassandra Sherrod, PROJECT MANAGER (301-594-1300) 8ンプ・ころぞう

Dear Sir Madam:

This facsimile is in reference to your abbreviated new drug/antibiotic application dated May 3,1976, submitted pursuant to Section 5050)/507 of the Federal Food, Drug, and Cosmetic Act for Seleni line indirectional Tablets USP, Sony.

Reference is also made to your amendment(s) dated Morch 10, 1997.

Attached are pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301-827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addresses or a person sutherized to deliver this document to the addresses, you are hereby notified that my disclosure, discensination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

X'new/ogdadmin/flutrak/faccov/fax

JUL 7 1997

38. Chemistry Comments to be Provided to the Applicant
ANDA: 74-912 APPLICANT: Stason Industrial Corp.

DRUG PRODUCT: Selegiline Hydrochloride Tablets, USP 5 mg
The deficiencies presented below represent Facsimile deficiencies.

Chemistry Deficiencies

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D. Director Division of Chemistry II Office of Generic Drugs Center for Drug Evaluation and Research



STASON INDUSTRIAL CORPORATION

11 MORGAN, IRVINE, CA 92718-2005, U.S.A. TEL: (714)380-4327 FAX: (714)380-4345

March 10, 1997

Office of Generic Drugs, CDER Food and Drug Administration Metro Park North II 7500 Standish Place Rockville, MD 20855-2773 THEHOMEN'S

Re:

ANDA 74-912, Selegiline Hydrochloride 5 mg Tablets

Reference is made to the chemistry and labeling deficiency letter dated January 30, 1997 for ANDA 74-912, Selegiline Hydrochloride 5 mg Tablets.

Enclosed, we have submitted a MAJOR amendment (Amendment #002) to resolve the deficiencies in the application as set forth in the deficiency letter.

Sincerely yours,

Harrv T.**∕**Fan

Chief Operating Officer

MAR 1 2 1997

GENERIC DRUGS



STASON INDUSTRIAL CORPORATION

11 MORGAN, IRVINE, CA 92718-2005, U.S.A. TEL: (714)380-4327 FAX: (714)380-4345

ANDA 74-912

Office of Generic Drugs, CDER Food and Drug Administration, HFD-650 Metro Park North II 7500 Standish Place Rockville, MD 20855-2773

May 12, 1997

Dear Sir,

Reference is made to the bioequivalence deficiency letter dated March 5, 1997 for ANDA 74-912 for Selegiline Hydrochloride Tablets, 5 mg. Enclosed we have submitted our Amendment # 003 to resolve the deficiencies in the application as set forth in the deficiency letter for our bioequivalence data.

Respectfully yours,

Chief Operating Officer

RECEIVED MAY 1 6 1997

GENERIC DRUGS

IAN 30 1997

MAJOR AMENDMENT

ANDNAMDA: 74-912

OFFICE OF GENERIC DRUGS, CDER, FDA Document Control Room, Metro Park North II 7500 Standish Place, Room 150 Rockville, MD 20855-2773 (301-594-0320)



TO: APPLICANT Stas on Industric Comptions (7/4) 380 - 4327
ATTN: Min Liang Pan FAX 7/4-380 - 4345

FROM: Kassadra Sherrod

PROJECT MANAGER (301-594-/3-0)

Dear Sir/Madam

This facsimile is in reference to your abbreviated new drug/antibiotic application dated May31,1995, submitted pursuant to Section 505(1/307) of the Federal Food, Drug, and Cosmetic Act for Selegitime Hydrochloride Tablets, Smg.

Reference is also made to your amendments dated August 21,1996.

The application is deficient and, therefore not approvable under Section 505/507 of the Act for the reasons provided in the attachments (14 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS: A hard copy of the labeling attachments (1 and 2) is being mailed under separate cover.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN REFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by talephone and return it to us by mail at the above address.

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JAN 3 (1 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-912 APPLICANT: Stason Industrial Corp.

DRUG PRODUCT: Selegiline Hydrochloride Tablets, USP 5 mg The following deficiencies represent MAJOR deficiencies.

A. Chemistry Deficiencies

באטר כשבת שטכן הווג די פני באטטיים · *U . CO--

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.

Director

Division of Chemistry I/II Office of Generic Drugs

Center for Drug Evaluation and Research

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REVIEW OF PROFESSIONAL LABELING DIVISION OF LABELING AND PROGRAM SUPPORT LABELING REVIEW BRANCH

ANDA Number: 74-912

عت ۱۵۰

Dates of Submissions: May 31, 1996 (RTF) August 21, 1996 (AC)

Applicant's Name: Stason Industrial Corporation

Established Name: Selegiline Hydrochloride Tablets USP, 5 mg

Labeling Deficiencies:

- 1. CONTAINER 60s and 1000s
 - a. "Each Tablet Contains" statement Insert a space between "5" and "mg".
 - b. Include the following "Dispense in" statement: Dispense in a tight, light-resistant container.
 - c. Storage recommendation Revise to read:

... temperature 150-300C (590-860F). [°C range to appear first]

2. INSERT

- a. Revisions are indicated in the enclosed "mock-up" of your proposed draft labeling. The model labeling for Selegiline Hydrochloride Tablets is the approved labeling of the listed drug, Eldepryl Capsules (Somerset Pharmaceuticals, Inc.; Approved May 15, 1996). A reference copy for your convenience is enclosed with your mock-up.
- b. Please assure your subsection headings are consistent in prominence throughout the insert. Some are underlined or followed by colons, others are not.

Please revise your container labels and insert labeling, as instructed above, and submit final printed container labels and draft insert labeling.

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Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Jecty Phillips

Director

Division of Labeling and Program Support

Office of Generic Drugs

Center for Drug Evaluation and Research

FNClosure

SELEGILINE HYDROCHLORIDE TABLETS, USP

DESCRIPTION:

Selegiline Hydrochloride is a levorotatory acetylenic derivative of phenethylamine. It is commonly

referred to in the clinical and pharmacological literature as I-deprenyl.

The chemical name is: (R)-(-)(N/2-dimethyl-10/2-propynlphonethylamine bydrochloride. It is a white to near white crystalline powder, freely soluble in water, chloroform, and methanol, and has a molecular weight of 223.75. The structural formula is as follows:

table! for cral administration Contains...

A New Sufficient

Each round, white to off-white tablet, embassed one side with "1020" and on the other side with "STASONE contains 5 mg selegiline hydrochloride. Inactive ingredients are microcrystalline cellulose, lactose monohydrate, and stearic acid Alphabet se

CLINICAL PHARMACOLOGY:

The mechanisms accounting for selegiline's beneficial adjunctive action in the treatment of Parkinson's disease are not fully understood. Inhibition of monoamine oxidase, type B, activity is generally considered to be of primary importance; in addition, there is evidence that selegiline may act through other mechanisms to increase dopaminergic activity.

Selegiline is best known as an irreversible inhibitor of monoamine oxidase (MAO), an intracellular enzyme associated with the outer membrane of mitochondria. Selegiline inhibits MAO by acting as a 'suicide' substrate for the enzyme; that is, it is converted by MAO to an active moiety which combines irreversibly with the active site and/or the enzyme's essential FAD cofactor. Because selegiline has greater affinity for type B than for type A active sites, it can serve as a selective inhibitor of MAO type B if it is administered at the recommended dose.

MAOs are widely distributed throughout the body, their concentration is especially high in liver, kidney. stomach, intestinal wall, and brain. MAOs are currently subclassified into two types, A and B, which differ in their substrate specificity and tissue distribution. In humans, intestinal MAO is predominantly type A, while most of that in brain is type B.

In CNS neurons, MAO plays an important role in the catabolism of catecholamines (dopamine, norepinephrine and epinephrine) and serotonia. MAOs are also important in the catabolism of various exogenous amines found in a variety of foods and drugs. MAO in the GJ tract and liver (primarily type A), for example, is thought to provide vital protection from exogenous amines (e.g., tyramine) that have the capacity, if absorbed intect, to cause a 'hypertensive crisis,' the so-called 'cheese reaction.' (If large amounts of certain exogenous amines gain access to the systemic circulation - e.g., from fermented cheese, red wine, herring, over-the-counter cough/cold medications, etc.— they are taken up by advenergic

neurons and displace norepinephrine from storage sites within membrane bound vesicles. Subsequent release of the displaced norepinephrine causes the rise in systemic blood pressure, etc.)

בווא טטע אשער יענע

Should be able to take In theory, therefore, because MAO A of the gut is not inhibited, patients treated with selegiline at a dose of 10 mg a day can take medications containing pharmocologically active amines and consume tyraminecontaining foods without risk of uncontrolled hypertension. To date, clinical experience appears to confirm this prediction; cheese reactions have not been reported in selegiline treated patients. The pathophysiology of the 'chaese reaction' is complicated and, in addition to its ability to inhibit MAO B selectively, scientime's appoint freedom from this reaction has been attributed to an ability to prevent tyramine and other indirect acting sympathornimetics from displacing norepinephrine from advenergic neurons. ,~ neurons. 🥎

However, until the pathophysiology of the cheese reaction is more completely understood, it seems prindent to assume that selegiline can only be used safely without dictary restrictions at doses where it presumably selectively inhibits MAO B (e.g., 10 mg/day). In short, attention to the dose dependent NEW nature of selegiline's selectivity is critical if it is to be used without claborate restrictions being placed on diet and concomitant drug use, (See WARNINGS and PRECAUTIONS.)

It is important to be aware that selegiline may have pharmacological effects unrelated to MAO B inhibition. As noted above, there is some evidence that it may increase dopaminergic activity by other mechanisms, including interfering with dopamine re-uptake at the synapse. Effects resulting from selegiline administration may also be mediated through its metabolites. Two of its three principal metabolites, amphetamine and methamphetamine, have pharmacological actions of their own; they interfere with neuronal uptake and enhance release of several neurotransmitters (e.g., norepinephrine, doparmine, serotonin). However, the extent to which these metabolites contribute to the effects of selegiline are unknown.

Rationale for the Use of Selective Monagamine Oxidase Type B Inhibitor in Parkingon's Disease: Many of the prominent symptoms of Parkinson's disease are due to a deliciency of striatal dopamine that is the consequence of a progressive degeneration and loss of a population of dopaminergic neurons which originate in the substantia nigra of the midbrain and project to the basal ganglia or striatum. Early in the course of Parkinson's, the deficit in the capacity of these neurons to synthesize dopamine can be overcome by administration of exogenous levodopa, usually given in combination with a peripheral decarboxylase inhibitor (carbidopa). Sista sa

With the passage of time, due to the progression of the disease and/or the effect of sustained treatment, the efficacy and quality of the therapeutic response to levodopa diminishes. Thus, after several years of levodopa treatment, the response, for a given dose of levodopa, is shorter, has less predictable onset and offset (i.e., there is 'wearing off'), and is often accompanied by side effects (e.g., dyskinesia, akinesias, onoff phonomena, freezing, etc.).

This deteriorating response is currently interpreted as a manifestation of the inability of the ever decreasing population of intact nigrostriatal neurons to synthesize and release adequate amounts of dopamine.

MAO B inhibition may be useful in this setting because, by blocking the catabotism of dopamine, it would increase the net amount of dopamine available (i.e., it would increase the pool of dopamine). Whether or not this mechanism or an alternative one actually accounts for the observed beneficial effects of adjunctive selegiline is unknown.

Selegitine's benefit in Parkinson's disease has only been documented as an adjunct to levodopa/carbidopa. Whether or not it might be effective as a sole treatment is unknown, but past attempts to treat Parkinson's disease with non-selective MAOI monotherapy are reported to have been unsuccessful. It is important to

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note that attempts to treat Parkinsonian patients with combinations of levodopa and currently marketed non-selective MAO inhibitors were abandoned because of multiple side effects including hypertension, increase in involuntary movement, and toxic delirium.

Pharmacokinetic Information (Absorption, Distribution, Metabolism and Ellmination—ADME):
Only preliminary information about the details of the pharmacokinetics of selegiline and its metabolites is available.

Data obtained in a study of 12 healthy subjects that was intended to examine the effects of selegiline on the ADME of an oral hypoghycemic agent, however, provides some information. Following the oral administration of a single dose of 10 mg of selegiline hydrochloride to these subjects, serum levels of intact selegiline were below the limit of detection (less than 10 ng/mL). Three metabolites, N-desmethyldeprenyl, the major metabolite (mean half-life 2.0 hours), implication (mean half-life 17.7 hours), and methamphetamine (mean half-life 20.5 hours), were found in screen and urine. Over a period of 48 hours, 45% of the dose administered appeared in the trine as these 3 metabolites.

In an extension of this study intended to examine the effects of steady state extensions, the same subjects were given a 10 mg dose of setegiline hydrochloride for seven consecutive days. Under these conditions, the mean trough serum levels for amphetamine were 3.5 ng/mL and 8.0 ng/mL for methamphetamine: trough levels of N-desmethyldeprenyl were below the levels of detection.

The rate of MACB regeneration following discontinuation of treatment has not been quantitated. It is this rate dependent upon de novo protein synthesis, which seems likely to determine how fast normal MACB activity can be restored.

INDICATIONS AND USAGE:

Selegiline Hydrochloride is indicated as an adjunct in the management of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. There is no evidence from controlled studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy.

Evidence supporting this claim was obtained in randomized controlled clinical investigations that compared the effects of added selegitine or placebo in patients receiving levodopa/carbidopa. Selegitine was significantly superior to placebo on all three principal outcome measures employed: change from baseline in daily levodopa/carbidopa dose, the amount of 'off' time, and patient self-rating of treatment success. Beneficial effects were also observed on other measures of treatment success (c.g., measures of reduced end of dose akinesia, decreased tremor and sialorrhea, improved speech and dressing ability and improved overall disability as assessed by walking and comparison to previous state).

CONTRAINDICATIONS:

Selegiline Hydrochloride is contraindicated in patients with a known hypersensitivity to this drug.

Selegiline Hydrochloride is contraindicated for use with meperidine (DEMEROL & other trade traines).

This contraindication is often extended to other opioids. (See, Drug Interactions.)

PERATIONS

WARNINGS:

Selegiline should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO. (See CLINICAL PHARMACOLOGY.)

The selectivity of selegiline for MAO B may not be absolute even at the recommended daily dose of 10 mg a day and selectivity is further diminished with increasing daily doses. The precise dose at which

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10:22

selegitine becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg a day.

Severe CNS toxicity associated with hyperpyrexia and death have been reported with the combination of tricyclic antidepressants and non-selective MAOIs (NARDIL/PARNATE). A similar reaction has been reported for a patient on amitriptyline and selegiline hydrochloride. Another patient receiving protriptyline and selegiline hydrochloride developed tremors, agitation, and restlessness followed by unresponsiveness and death two weeks after selegiline hydrochloride was added. Related adverse events including hypertension, syncope, asystole, disphorosis, seizures, changes in behavioral and mental status, and muscular rigidity have also been reported in some patients receiving selegiline hydrochloride and various tricyclic antidepressants.

Serious, sometimes fatal, reactions with signs and symptoms that may include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations of the vital signs, and mental status changes that include extreme agitation progressing to delirium and coma have been reported with patients receiving a combiantion of fluoxetine hydrochloride (PROSAC) and non-selective MAOIs. Similar signs have been reported in some patients on the combination of selegiline hydrochloride (10 mg a day) and selective serotonin reuptake inhibitors including fluoxetine, sertraline and paroxetine.

Since the mechanisms of these reactions are not fully understood, it seems prudent, in general, to avoid this combination of selegiline hydrochleride and tricyclic antidepressants as well as selegiline hydrochleride and selective serotonin reuptake inhibitors. At least 14 days should etapse between discontinuation of selegiline hydrochleride and initiation of treatment with a tricyclic antidepressant or selective serotinin reuptake inhibitors. Because of the long half lives of fluoretine and its active metabolite, at least five weeks (perhaps longer, especially if fluoretine has been prescribed chronically and/or at higher doses) should elapse between discontinuation of fluoretine and initiation of treatment with selegiline hydrochleride.

PRECAUTIONS:

General:

Some patients given selegiline may experience an exacerbatign of levodopa associated side effects, presumably due to the increased amounts of dopamine reacting with super/sensitive post-synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa/carbidopa by approximately 10 to 30%.

The decision to prescribe selegiline should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with selegiline. Consequently, the full spectrum of possible responses to selegiline may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe patients closely for atypical responses.

Information for Patients

Patients should be advised of the possible need to reduce levedops dosage after the initiation of selegiline hydrocklarket therapy.

Patients (or their families if the patient is incompetent) should be advised not to exceed the daily recommended dose of 10 mg. The risk of using higher daily doses of selegitine should be explained, and a brief description of the 'choese reaction' provided. While hypertensive reactions with selegitine associated with dietary influences have not been reported, documented experience is limited. Consequently, it may be useful to inform patients (or their families) about the signs and symptoms associated with MAOI induced hypertensive reactions. In particular, patients should be urged to report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced.

Non Constitution

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reaction (spelling)

CASC ...

No specific laboratory tests are deemed essential for the management of patients on selegilinic. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions

The accurrence of stupor, muscular rigidity, severe agitation, and elevated temperature has been reported in some patients receiving the combination of selegiline and meperidine. Symptoms assally resolve over days when the combination is discontinued. This is typical of the interaction of meperidine and MAOIs. Other serious reactions (including sovere agitation, hallucinations, and death) have been reported in patients receiving this combination (see CONTRAINDICATIONS). Severe toxicity has also been reported in patients receiving the combination of tricyclic antidepressents and selegiline hydrochloride and selective serotonin reuptake inhibitors and selegiline hydrockforide. (See WARNINGS for details.)

Carcinogenesis, Mutagenesis, Adi Impairment of Fertility:

Studies have not been performed to date to evaluate the carcinogenic potential of selegiline hydrochloride.

Pregnancy: Terestoginic Effects

Pregnancy Category C. Insufficient animal reproduction studies have been done with selegiline to conclude that selegiline poses no teratogenic risk. However, one ret study carried out at doses as much as 180 fold the recommended human dose revealed no evidence of a teratogenic effect. It is not known whether selegiline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Selegiline should be given to a pregnant woman only if clearly needed.

Nursing Mothers:

It is not known whether selegiline hydrochitoride is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women. me "pedicinic patients"
rather isaa "Chilora"

Pediatric Use:

The effects of selegiline hydrochloride in children have not been evaluated.

ADVERSE REACTIONS:

Introduction:

The number of patients who received selegiline in prospectively monitored pre-marketing studies is limited. While other sources of information about the use of selegiline are available (e.g., literature reports, foreign post-marketing reports, etc.) they do not provide the kind of information necessary to estimate the incidence of adverse events. Thus, overall incidence figures for adverse reactions associated with the use of selegiline cannot be provided. Many of the adverse reactions seen have also been reported as symptoms of dopamine excess.

Moreover, the importance and severity of various reactions reported often cannot be ascertained. One index of relative importance, however, is whether or not a reaction caused treatment discontinuation. In prospective pre-marketing studies, the following events led, in decreasing order of frequency, to discontinuation of treatment with selegiline: nauses, halhucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increused akinetic involuntary movements, agitation, arrhythmia, bradykinesia, chores, delusions, hypertension, new or increased angina pectoris, and syncope. Events reported only once as a cause of discontinuation are ankle edoma, anxiety, burning lips/mouth, constitution, drowsiness/lethargy, dystonia, excess perspiration, increased freezing, gastrointestinal bleeding, hair loss, increased tremor, nervousness, weakness, and weight loss. ے اسرہ 19 خالساند

Experience with selegiline obtained in parallel, placebo controlled, randomized studies provides only a limited basis for estimates of adverse reaction rates. The following reactions that occurred with greater frequency among the 49 patients assigned to selegiline as compared to the 50 patients assigned to placebo

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in the only parallel, placebo controlled trial performed in patients with Parkinson's disease are shown in the following Table. None of these adverse reactions led to a discontinuation of treatment.

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INCIDENCE OF TREATMENT-EMERGENT ADVERSE EXPERIENCES IN THE PLACEBO-CONTROLLED CLINICAL TRIAL

1HE I	THE PLACEBO-CONTROLLED CLINICAL TRIAL				
Adverse Event	Number of Patients	Number of Patients Reporting Events			
	selegiline hydrochloride	placebo			
X 9	N=49	N=50			
Nausee	10	7			
Dizziness/Lightheaded/Fainting	3 7	ī			
Abdominal Pain	4	2			
Confusion	3	4			
Hallucinations	3	1			
Dry mouth	3	1			
Vivid Dreams	2	1			
Dyskinesias	2	O .			
Headache	2	3			
The following events were read	orted eace in either or both groups				
Ache, generalized	a see secs or cities or posts proubs				
Anxiety/Tension	1 1	0			
Anemia	1	l			
Diarriea	•	1			
Hair Loss	1	0			
Insomnia	0	i			
Lethergy	1	ŧ			
	1	O			
Leg Pain	l	Ŏ			
Low back pain	. 1	ò			
Malaise	0	i			
Palpitations	1	'n			
Utinary Retention	1	0			
Weight Loss	1	a			

In all prospectively monitored efinical investigations, enrolling approximately 920 patients, the following adverse events, classified by body system, were reported.

Central Nervous System:

Motor/Coordination/Extrapyramidal:

blepharospasm (chelling)

increased tremor, chorea, loss of balance, restlessness, blephérospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch*, myoclonic jerks*, stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps.

Mental Status/Behavioral/Psychiatric:

hallocinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, droams/nightmares, tiredness, delusions, disorientation, lightheadedness, impaired memory*, increased energy*, transient high*, hollow feeling, lethergy/malate, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability

Pain/Altered Sessation:

headache, back pain, leg pain, timaitus, migraine, supraorbital pain, throat burning, generalized sche, chills, numbness of toes/fingers, taste disturbance.

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Autonomic Nervous System:

dry mouth, blurred vision, sexual dysfunction.

Cardiovascular:

والحاربين برون

orthosiatic hypotension, hypertension, arrhythmia, palphations, new or increased angina pectoris. hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope.

Gastrointestinal:

nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism*, gastrointestinal bleeding (exacerbation of preexisting ulcer disease).

Genitourinary/Gynecologic/Endocrine:

slow urinstion, transient anorgasmia*, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile seasations, urinary frequency.

Skin and Appendages:

increased sweating, disphoresis, facial hair, hair loss, hematoma, rash, photosensitivity.

Miscellaneous:

asthma, diplopia, shortness of breath, speech affected.

Postmarketing Reports:

The following experiences were described in spontaneous post-marketing reports. These reports do not The following experiences were described in spontaneous provide sufficient information to establish a clear causal relationship with the use of selegitine.

CNS:

Scizure in dialyzed chronic renal failure patient on concomitant medications. indicates events reported only at doses greater than 10 mg/day.

OVERDOSAGE:

Selegiline:

No specific information is available about clinically significant overdoses with selegitime. However, experience gained during selegiline's development reveals that some individuals exposed to doses of 600 mg d.l-selegiline suffered severe hypotension and psychomotor agitation.

Since the selective inhibition of MAO B by selegiline hydrochloride is achieved only at doses in the range recommended for the treatment of Parkinson's disease (e.g., 10 mg/day), overdoses are likely to cause significant inhibition of both MAO A and MAO B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed non-selective MAO inhibitors [e.g., tranyleypromine (MARPEAN), and phenelzine (NARDIL).

ISOCArboxezid" (FIElling) Overdose with Non-scientive MAO Inhibition:

NOTE: This section is provided for reference; it does not describe events that have actually been observed with sclegiline in overdose.

Characteristically, signs and symptoms of non-scientive MAOI overdose may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndroms may not be reached for upwards of a day following the overdose. Death has been reported following overdosage. Therefore, inumediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion of such drugs in overdose, is strongly recommended.

The clinical picture of MAOf overdose varies considerably; its severity may be a function of the amount of drug consumed. The central nervous and cardiovascular systems are prominently involved.

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Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headnche, hallucinations, trismus, opisthotomus, convulsions, and como, rapid and irregular pulse, hypertension, hypotension and vascular collapse; precordial pain, respiratory depression and fallure, hyperpyrexia, diaphoresis, and cool, clammy skin.

Treatment Suggestions For Overdose:

NOTE: Because there is no recorded experience with sciegilise overdose, the following suggestions are offered based upon the assumption that actegitine overdose may be modeled by non-selective MAOI poisoning. In any case, up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physicians' Deak Reference (PDR).

Treatment of overdose with non-eslective MAOIs is symptomatic and supportive. Induction of emesis or gastric lavage with instillation of charcoal shurry may be helpful in early poisoning, provided the airway has been protected against aspiration. Signs and symptoms of contral nervous system stimulation, including convulsions, should be treated with diazepam, given slowly intravenously. Phonothiazine derivatives and central nervous system stimulants should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids and, if necessary, blood pressure titration with an intravenous infusion of a dilute pressor agent. It should be noted that adrenergic agents may produce a markedly increased pressor response.

Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventiletory assistance, as required.

Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.

Selegiline hydrochloride Tablet are intended....

DOSAGE AND ADMINISTRATION:

... Selegiline-is-intended for administration to Parkinsonian patients receiving levodopa/carbidopa therapy who demonstrate a deteriorating response to this treatment. The recommended regimen for the administration of selegiline is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and funch. There is no evidence that additional benefit will be obtained from the administration of higher doses. Moreover, higher doses should ordinarily be avoided because of the increased risk of side - Ladrack lovide

After two to three days of selegiline treatment, an attempt may be made to reduce the dose of levodopa/carbidopa. A reduction of 10 to 30% was achieved with the typical participant in the domestic placebo controlled trials who was assigned to sciegiline treatment. Further reductions of levedops/carbidopa may be possible during continued selegiline therapy.

mydruchlunde HOW SUPPLIED:

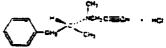
Selegiline lablets are available containing 5 mg of selegiline hydrochloride. Each white to off-white, round, unscored tablet is embossed with "1020" on one side and "STASON" on the other side.

They are available in bottles of 60 tablets and 1000 to Store at controlled room temperature (59° to 86°F) (1	ableta Sec 5° to 30°C). Con	letter. Comment und Taimeil,	£.2	•
CAUTION—Federal (USA) law prohibits dispension Selegiline Hydrochloride tablets are manufactured by Literature issued May, 1996.	without prescription. Stason Pharmaceutics	als, Inc. Revi	k applead	om pala
Literature issued May, 1996.	•	2530	7 600	"MHE 6"
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PLOTTER, (Milaphine hyperchannel of 8 Novementry acceptance derivative of amendmentees it is community sourced to it the change and pharmacological situations as 1-ascrepty.

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The chemical name is: (R1-(-)-R2-dimension-N-2-propping beneathy-Issued hydractionide. If is a water to hear white properties condex, they cause in wear, properties, and principal, and has a molecular to the properties. weight of 221.75. The structural formula it as motors:



Each adul blue consult is Sand imprinted with the Sameraer togo on Can and "Cleany) 5 mg on the awy. Each pressin equipment 5 mg selegiting hydrochlorids. Inspires information and color acid. Income, magnesium standard, and incomergephon that can. ne 5 mg

CLINICAL PRARMACOLOGY.

The mechanisms accounting for satisfance business experience action in the treatment of Perhapson's climate are not funly uncorrected, benefits bites of monocome excess. Spc &, acres; 3 generally control of primary importance; is 300ton, there is ordered that a may set through other mechanisms is moreous accommunged activity.

Salegation is sent import as an impropriate inhabitor of monograms and date (MACD), an intracellular anaesse associated with the outer monograms of informatria. Selegation inhabits AAO (2) acting as 8 (selection substitute for the grapme; (Ball is, it is converted by AAO to all actions monety which combines irreversibly with the active site engler the enryme's essential FAD confector, decayes asseption has greater efficity for type 8 rather than for type A active sizes, it can some as a selective beneable at hit is easy DAM: to which nd at the qu

MAOs are windly distributed throughout the teste their concentration is assessed, high in liner, history, assessed, interested wind, and brain. MAOs are currently subclassified into the open. A and B, which gifter in their substrate specifically and traum distribution, to remove, intentinal MAG as precominantly type A, while most of tray in grain is type ${\bf Q}_{\rm c}$

in CHS nearons. MAID plays an element rate in the catabolism of cata-chalamines following, narepated view are some crewal and services. MAIS 479 2410 important in the catabolism of various designment anames formed in a variety of familia and drugs. MAC in the GF tract and fiver (primarily type A), for example, is thought to provide with protoc-THE INVESTMENT THE ALTO EXECUTE A TOMBET TO PROPER WITH PRESCRIPTION FROM CONTINUES ARTHURS (e.g., tyramines trace have the Capacity, if assured exect, to cause a hyperspecture critical the se-casted critical residences. It is pre-casted critical residences are the systems criticalsten — e.g., from formation criticals, and make, butring, over-the-awards coughcadd medications, etc. - they are taken up by advance; securing and distinct integrations, etc. - they are taken up by advance; securing and distinct integrations from astronge sites within flucturate boung resident. Subsequent release of the dispraced appearance causes the rise in systemic place procure, etc.)

in theory, since GAD A of the But is not contained, potients brance with speguine at a does of 10 mg a day shows as agis to take medications contenung pharmacougically active amines and contenue tyramice-contenung foods without risk of incontrolled hypercension. However, one case of importanging crisis has been reported in a patient taking the recommended done of straption and a sympothemination models— 100 (canadrina). The \$1(7000) saling of the "merce reaction" is conplicated and, in addition to its abouty to innibit MAO B salestively. smeghines relative fraction from this reaction has been estributed to samplines relative treates from this reactive has been obtributed to an ability to present cyrumine and other indirect acting sympathemisectrics from despisacing nareprespencie from admissiple desponsional flowers, with the palloophysiology of the cross-electrical in more despisably understand, it seems product to assume that integrate can ordinarily only so used safety without distance restrictions at doses where it presentably substitutely imports MAO 8 (a.g., 10 mg/cm).

in short, attestion to the desc dependent nature of salegillar's salectivity is critical if it is to be used utilized consumptions of the salectivity is critical if it is to be used utilized on attempt, as noted being placed on allot and concentrate stry can attempt, as noted above, a case of hypothesians while his been repurched at the recommend dead, (See MARSHINGS and PRECASTICES.)

It is important to be owere that adequise may have phermeaningcal effects wareless to MACI B inhibition. As noted above, those is some tridence that it may increase desominate activity by other macha-nities, including interfering with desomine re-unitate at the systems. In I DE EXEMPLING INTERFERENCY WAS INCOMEDIATED AND THE SYMPOSITION OF THE SYMPOSITION OF THE STATE OF THE SYMPOSITION OF THE S Il neurorangement (e.g., soreprophene, dynamics, personnis). Mystere the extent to which these meropolitis contribute to the effects of

Rationale for the tips of a Salective Monoamies Galdane Type B million in Paralmen's Despot: Many of the problems sumetens of Paralmen's Despate are sun to a descript of strated department that is the consequence of a progressive segmention and has of a population

of declarances: readers which originate in the substantia sugar of the minerals are expect to the basel gargine or structure. Early in the course of Paramete & Dictions. The delical in the commony of those new-TARS TO OPERATE SEES MADE CAN BE STANDARD BY ADMINISTRACION OF MORPHOSE STANDARD STA

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with the pessive of burs, due to the progression of the disease and/or the effect of sustained treatment, the efficiety and quality of the thora-PUTCH TOSPONSE TO INVOICEMENT GUTUNISHES. These after several years of leverage treatment, the response, for a green dose of low STOTEM. HOS less projectable enset and offset fi.e. There is "leading off"), and is often accompanied by side offsets (e.g., dyseniesis, spinos-344, sn-off the openies, branes, etc.).

This delanatating residesa is currently interpresed as a meni The inchinity of the aver decreening population of integer automorphisms in neurons to Synthesian and disease administry amounts of 3000mins.

1640 & selection may be useful in this setting because, by binching the Catabolism of the man, if word increase to an amount of decimal, as well increase in a amount of decimal, as well increase the new amount of decimals as-leading like, if what increase the year of decimals the first or net this means or at a second control of the decimal according for the decimal decimals of decimal that the decimal decimals of decimals of decimals and decimals.

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Phormocokinutic intermation (Absorption, Bratribution, Metabo isetien ADMED.

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Single and acce station do not product myltigia dese sinetics, is At study stare the year playma level or surgetime is 4 feld that octained telephone a single does introduce concentrations increase in a lesser educe, overaging 2 feld that soon after a pingle does.

The tensoralisticity of sategriline is increased 3 to 1 followhen it is taken with food.

The estant of transpare immassive to selegitime at a given done varies con-aderably among individuals. Estimates of systemic cuestrating of estag-line are not provided. Following a single trail done, the mean estimates half-life of selegitime is two hears. Under 210,300 state conditions the dimension harf-its increase is the liner.

Because samplimes inhibition of MACO-B is irroversible, it is unpressible to Stocket the around of MACO-B inhibition from steady state pleases investigated from the state of the state of the states als. For the same reason, it is not passible to predict the rate of race of MAG-6 activity as a function of plasma levels. The recovery of MAG-8 accounts as a function of the name problem symphosis; however, information of the name of the name problem symphosis is not yet overliable. Although mostlet leads. B activity returns to the normal range under 5 to 7 days of sneghtne discontinuouse, the leatings between purpose and trains MAG. B inhabition at not fully endorshed nor is the relationship of MAG. B inhabition in that fully endorshed nor is the relationship of MAG. B inhabition to the currical affect established (see CARCS) Pharmacologic.

Special Papalacture:

No pharmocolenets information is available on mateginne or its musabe-lites in rangity important subjects.

Hepatic Impermant: Pla Phorhacolinges: information is avoidable on solog-time or its Mutaeu-line of Beautically impoved solyets.

Attending a general conclusion aspect the effects of age on the pharmo-collection of sampless as a supplement secretar at the sum of the sam-pre evolution (12 subjects greater than 60 spars of age. 12 subjects between the stees of 18 to 30% spanner commission and about home as great in older as compared to a passignr psychology great 4 single and 0000 of 16 mg.

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MANAGEMENT AND WARE

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ELDEPHYL is contransficulted for use with mappinshina (REMERICA & armin 1999 ANGERS. This contransficultion is client accessed to under species (Ses Oraș Interacatas)

CONTRAMBICATIONS.

Energitime should not be used at duly dema encouring these recom-mondate (16 mg/day) because of the ricks associated with nea-conoctors insulation of MAS. (Los CLIMICAS, PRANSACTIONS)

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SETTITE CAS COLUCILY EXECUTIONS with Injurity-time and distill have been reported with the consumption of trayers 140-year-25453 and emperiod MADIO PARKEL PARKELS A senior disches has been reserved in a carrier on a senior and ELECTRIX. Assume annual disches ing subtraction and CLIDETH, document, and experience of the control of the contr status, and muscular regular have also been remitted at about gardent tocomeny ELDERYL and various district ancogniciants.

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PRECAUTINES.

Some detients given selegilies may experience on inscerbation of layadams asseciated side effects, presumptly due to the increased armounts of departmen macroin with super sadontine, post-ownests; receptors. These effects may often do intogeted by reducing the dead of avodona/emissage by approximately 18 to 50%.

The decrains to preachin unlegitine should take into consciousion that the NACO system of engines is complex and incomplexely uncertaint and there is enty a limited account of complex decreased limited accounts of consciousion of the stage clearly for Alburchi no

Information for Policeto

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Liberatory Radio:

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The occurrence of stopps, meadcular riginals, source agricums, and cloud-ou comparature has been reported at some persons receiving the comb-nation of salegi-1: and measurement. Speakings observe source over some when the commences in descentioned. There is Dorton the intercom-of measurement and MANNE, Other services mechanic personal grown agr-134mm, hasteringstown, and death) have been 1250/38 or patients not left this compression too ESSTRAMMOCENERS. Shown beingly nos o one meaned in assesse recovery the combination of inciplin anisisats and ELBEPRYL and selective selections respease inhibitors and ELDEPHYL (See WARRINGS for delaifs) One case of Inportensive THE CLASSIFICATION OF THE PROPERTY OF THE CONTROL OF T

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The offect of seregime on fertility has not been adequately essessed.

ancy Cavegory C: No terestageniz offects were disserved in a all bryo-fetal development in Sozagua-Damey fets at ami dates of nent in Scragus-Denney /ets at oral de 12, and 36 mg/kg or 4, 12 and 35 times the number theremouse does or a major book. No revergence oriests were observed in a study of antispo-fetal development in they Zonland White rabbits at grad design. 5, 25, and 50 mg/kg or 10, 48, and 95 pines the human therapeutic dese on a mg/m! cases, however, in this study, the neon or of 140012 Avoduces at the two higher doses was loss than recon maries for H the state of the s the recommendation of a personal commendation with a register does resided, in a summer of the facultat part development shock on Serague-Daviey rate local development shock of Serague-Daviey rate local development of 4, 16, and 54 mg/kg or 1, 15, and 52 meas the number thereprofit does on a majoral bases, an interme or no munder of somewhat and doctors in the number of somewhat and doctors in the number of some or dam, her somewhat, and but body worght lat birth and tursuspiced the lateration periods were absented at the less legislat does a. At the highest door bested, no negletic side survived to they a deep the highest door bested, no negletic side survived to they a deep the highest door bested, no negletic side survived to they a deep the highest door bested, no negletic side survived to they a deep the highest door bested, no negletic side survived to they are neglected. Passatta and advisorment at the Adjusts one basins in dank could not be evaluately severation at the lock of surviving guids. The reproductive performance of the unbounted offturne was not stream!

There are no adequate and meli-controlled studies in programs values. Satisfilms should be used during programmy only if the potential benefit justified the potential right to the letter.

R is mit beginn whicher selegible hydrochlorde is excreted in human mile. Because many drugs are screens in human mile, consideration should be given to discontinuing the use of all but abandulary additional ats at nursing women.

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The effects of smagnine hydrocoloude in children have not been evaluat-

ADVERSE REACTIONS:

for the company of patents who received selegating in prospectively monitored pro-marketing studies is limited. While cond sources of intermetrial about the easy of sologiting are available for 2. However, reports, forsign past-marketing records, etc.) they do not provide the kind of migrsign passives seeing records, etc.) anny ou are provided ion single or inver-nation decision figures for advance Pastiens: 2006-1466 with the list of coupling cannot be provided. Many of the Advance reactions: 3008 have also been reterrise as symptoms of decisions excess.

Margurer, the importance and severity of various rescribes reported offen cannot be accurated. One under a solitive imperance, however, is whether or not a reaction caused treatment discontinuation. In 19 waterier or not a reaction course treatment inscrimingulari, in presenting pre-marketing studies, the belond deserts ag, in decrea-ng order of Hangarity to discontinuation of treatment with selegione. National, harboristations, confission, deserts on, but of belonce, imper-nation, harboristations, increased absorbet involutiony individuals. 49. Citation image nal, orthogosic symmension, increases almanic instrument, increases agrantum, arthyrindus. Dradyslogista, Chorus, distribute, hypertension, new or increases displayed apply accepts, and species. Events inported unly sect as a cause of discontinuation are unles along, among, burning lephinosis. Consideration, displayerspathering, dystonia, access outsighted. Consideration of the consid 44. and waters have

Expensace with ELBERTYL obtained in parents, placebe conti Charmance was construct, automate as parama, pracesso conformed, ren-sionand status provides only a luminor social for estimates of asverse reaction rates. The tolerong reactions that escured with greater ba-quancy among the 49 patients assigned to salegated as communed to the 50 paramits assigned to placetto us the only paramet, placeton-assembled. Trail meriarated of patients with Parliments distance are shown in the for-

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ioning Table. Name of crasps sociates reactions, led 19 a discontinuestion of Treatment.

UICIDOICE OF THEATMENT. EMERGENT MOVERNE EXPERIENCES IN THE PLACENG-CONTROLLER

Adverse Event	Humber of Patients Reporting Equats					
•	riogitale hydrosoloni					
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Outness/Lighthandes/Fare	neg 7	l				
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in the prospectively monitored control investigations, evening apprecia #378'y 324 Socients, the lightning advance events, executi

Contro Herves System Motor/Coordination/Largeyra

ncreases symes, charea, less of balance, restinguest, blowing normen braspiceria, facial grinaca, falling down, many leg, musch niterii, miacanic jurisii sirri nacu, taronis dyslandia, dyslanic symp COME, Gyshinesia, involuntary movements, transing, lestination, is-Craded apraids, muscle premos.

Hants Status Hebriaral Psychiatric:

hartessations deziness confision, snooty, degración, drawsiness, heritantess, disposes, desarrangements, breatess, disposes, degrarativos change, desarrangements, important memory, increased servicionales, important memory, increased servicionales, increased servicionales, desarrangements, participation, servicionales, servicionales,

Pain/littered Sen

nesdoche, back pain, leg paid, tineltus, migrains, gupracraitel pain, threat burning, generalized ache, chilic, numerous of techniques, tasse

Autonomic Rervous System

dry mouth, blurred vision, terms dysfunction.

Cardiovescolar: Officialistic hydernamm, hypertansion, arrhythmia, pelokacions, new or increased angule pectaris, hypertansion, tectificardel, perioheral edema. SITUS BYROYCETÉIS. SYNCODE.

Costraintestia

n'escareprising, constitution, vergit loss, anoronie, paor appetie, oysphagis, diarrien, bearthum, rectal benoing, brasium", gastron-lustinol blooding (exacerboton of processing etter diagna).

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Thin and Appear

ned expecting, disphoracie, facial hair, hair loss, herhalama, rasa.

assume, diplome, shortness of practs, speech affected.

morkeling Reports:

The following imperiences were described in seemble ingresorts. These reports on not provide sufficient in Mail Seet-market. M information to estabhan a com course defendable such the see of STOEAGL

Seizure in dialyzed civance range faiture patient on concomitant mad-

indicates process reported only at doors greater than 18 ma/day. DVEDERELL.

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Parkacens disease to z . Its expellent countries and which to $(1-32) \pm \frac{1}{2}$ and carry unknown at 1200 A and NATO B. Correction to the 0.078 and COMES OF CONTRACT MAN ASSESSED THE VALUE OF THE PARTY OF PANSANG THE DAMESTIC GRACE!

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Respiration should be Eugenited by appropriate measures, including of all the steady ries of chebbarrans solder 196 mana. CO VERTICAL PROPERTY SECURED

Body temperature should be monitored classic intensive managemer of experipressa may be required. Maintenance of fixed and electronic

DOSACE AND ADMINISTRATION.

PERSONAL US intended for administration of Portinsonian Battering County by the County and Service and 5 mg each space at treatifest and tenen, face as to evening that to tenend tareff will be obtained from the appropriation of higher access Moreover, higher doses should ordinarily be avoided occause of the Actual risk of side effects.

After two to three days of selegition treatment, an actempt may be made After the to use ways in programs (reasonally, an account may be easily to endous the does of investmentations). A reduction of 10 to 30% will achieve with the based performant in the democracy placate contents: triple who was assigned to solutions trained. Further reductions of everage/corbidops may to preside during continues to regime the MAN MAPPLES.

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AGC 36586-622-60 betters of 60 courseles. AGC 36506-622-30 better of 300 courseles

Stare at compeled more temperature, 50° to 86°V .:5° to 30°C; CASTICH—Federal RISAI the provibits discouring without prescrit-



Ulterature rassest May 1996 20-89